SUMMARY MINUTES

OF THE

MICROBIOLOGY DEVICES

PANEL MEETING

OPEN SESSION

March 7, 2002

Gaithersburg Holiday Inn
Gaithersburg, MD

Attendees
Microbiology Devices Advisory Panel Meeting
March 7, 2002

Microbiology Devices Panel
Michael L. Wilson, M.D., Chair
Denver Health Medical Center

Kathleen G. Beavis, M.D.
Cook County Hospital

Margo A. Smith, M.D.
Washington Hospital Center

Stanley M. Reynolds
Consumer Representative
Pennsylvania Department of Health

Panel Consultants
Irving Nachamkin, Dr. P.H.
Hospital of the University of Pennsylvania

Valerie L. Ng, Ph.D., M.D.
San Francisco General Hospital

L. Barth Reller, M.D.
Duke University Medical Center

Lauri D. Thrupp, M.D.
University of California, Irvine

Carmelita U. Tuazon, M.D.
George Washington University Hospital

Ronald J. Zabransky, Ph.D.

FDA Personnel
Steven I. Gutman, M.D., M.B.A.
Director, Division of Clinical Laboratory Devices

Freddie Poole
Panel Executive Secretary

Roxanne Shively, MS
Sr. Review Scientist, Bacteriology Branch, Division of Clinical Laboratory Devices

OPEN SESSION

Panel Chair **Michael L. Wilson, M.D.,** called the meeting of the Microbiology Devices Panel to order at 10:37 a.m. and asked the panel members to introduce themselves. Panel Executive Secretary **Freddie Poole** then read the conflict-of-interest statement. She noted that **Kathleen G. Beavis, M.D**., and **Margo A. Smith, M.D.,** reported interests in firms at issue, but in matters not related to the topic in today's agenda. The agency determined that they may participate fully in all deliberations.

Concerning old business, Ms. Poole stated that on November 28, 2001, Sepsis Inc.'s Endotoxin Activity diagnostic assay had been found not approvable in concurrence with the panel's recommendations in its October 11, 2001, meeting and that the Osmetech urinary tract infection analyzer had been found substantially equivalent but with restrictions for its use. Cellestis Limited's QuantiFERON-TB device had been approved subject to the recommendations made by the panel in its October 12, 2001, meeting.

Dr. Wilson then stated that the charge to the panel was to classify several pre-1976 amendment devices to identify *Bacillus anthracis* and *Yersinia pestis.*

FDA Presentation: *B. anthracis*

Roxanne Shively, MS, Sr. Review Scientist, Bacteriology Branch, Division of Clinical Laboratory Devices, described the *B. anthracis* preamendment products, which aid in the diagnosis of anthrax in humans. She noted that the products are distributed primarily to public health laboratories and other

specialty laboratories that perform the tests on human specimens. Ms. Shively emphasized that the panel could choose to classify the three products separately. She described the three products, which consist of a specific bacteriophage ("gamma phage"), antibody conjugates, and antigens for antibody detection, and factors affecting each. Factors affecting gamma phage results include the behavior of variant phage strains, phage titer and stability, the media used, and the length of incubation, the inoculum density, and technologist experience.

Factors affecting fluorescent antibody conjugate results include the fact that capsular and cell-surface antigens of *B. anthracis* are shared by other species, the difficulty of preparing high-titer antisera in animals, growth conditions affecting encapsulation, and inoculum density.

Factors that affect the antigen reagent results obtained with the antigens include purity and concentration of the antigen preparation, prozone effects, subjective endpoints, nonspecific reactivity, abrogated antibody response due to antibiotic treatment, inability to differentiate recent and past infection, and prior vaccination.

In concluding, Ms. Shively provided some information on the historical use of the antigen test and noted that diagnostic laboratory testing for *B. anthracis* is limited to specialized and public health laboratories; the reagents are prepared for and distributed among those laboratories. She noted that although human disease is rare, *B. anthracis* is classified as a Category A "critical biological agent" because it can be easily disseminated and can cause high mortality.

Ms. Shively reviewed the classification process and described the types of controls that could be placed on devices to minimize risk to public health. She noted that a variety of regulations exists that apply to tests on or with *B. anthracis*, such as organism-specific practice guidelines from the Centers

for Disease Control and Prevention (CDC); local, State, and national reporting requirements; and the Select Agents Rule, which limits quality-control materials for vaccine strains.

Dr. Wilson then invited the panel to question Ms. Shively. **Carmelita U. Tuazon, M.D.,** asked whether Ms. Shively had any information on problems with the use of the reagents. Dr. Wilson asked **John W. Ezzell, Ph.D.,** Chief, Special Pathogens Branch, U.S. Army Medical Research Institute of Infections Diseases **(**USAMRID), who was in the audience, to respond. Dr. Ezzell answered that no false-positive or -negative results had been seen with the gamma phage using isolates but that low numbers of false positives had been reported with bacilli not normally associated with those clinical materials. Other criteria, however, can be used to differentiate results. **Stanley M. Reynolds** asked whether the gamma phage test was meant to be a stand-alone test, and Dr. Ezzell replied that it was not. Panel members asked for clarification on the commercial availability of the tests, the source for CDC's and USAMRID's strains, and the stability of the strains over time, which Dr. Ezzell answered to their satisfaction.

L. Barth Reller, M.D., raised the issue of whether laboratories outside the public health system should have access to the gamma phage. **Dr. Ezzell** noted that it could be useful for Level A (e.g., hospital) laboratories to have access to a quick-screen mechanism. Dr. Reller asked whether, given some of the pitfalls associated with control strains, it would be a good idea to put tests in the hands of inexperienced laboratories. Dr. Ezzell noted that the gamma phage is not used in any laboratory without proficiency testing and documentation and thought that it could be used in Level A labs. **Lauri D. Thrupp, M.D.,** concurred with Dr. Reller; he noted that when dealing with inexperienced laboratories and a low-prevalence organism, a hazardous situation could develop. Dr. Ezzell reiterated that the tests are largely unavailable outside the public health system and are distributed

through CDC. **J. Edward Brown, Ph.D.,** Chief, Quality Systems Integration, USAMRID**,** added that military laboratories obtain their reagents from CDC. Panel members continued discussion on whether it would be appropriate to use the tests in Level A laboratories. Dr. Ezell noted that certain Level B laboratories can use PCR techniques to ascertain the presence of *B. anthracis*, but gamma phage tests provide a quick screen, giving results within 4 to 5 hours; also it is unclear how widespread PCR techniques ultimately will become.

Open Public Hearing

John Ticehurst, M.D., Assistant Professor of Pathology and Medicine, the Johns Hopkins University School of Medicine**,** asked the panel members to think about the implications of false or improperly interpreted results and noted that in a biothreat situation, stand-alone use would be important because laboratories would be under pressure to provide rapid results. He noted the unique epidemiology of bioterrorism events and stated that the number of "worried well" would be likely to outnumber the number of actual patients. He asked the panel to be wary of classifying the devices in Class I or III, to insist on manufacturing consistency, and to restrict clinical use through gate keeping. Dr. Ticehurst noted that public health labs were overburdened during the anthrax incidents last fall and that many Level A labs have considerable expertise.

Dr. Wilson then invited the panel to question the speaker. **Dr. Reller** stated that the public health labs were overwhelmed because they were undersupported. He suggested strengthening Level B labs and enlarging their mission. He noted that in North Carolina, selected laboratories are asked to provide personnel to assist State public health laboratories and that the State relies on certain Level A

labs for consultation. The panel continued with a spirited discussion of the role of public health laboratories and the impact of using Level A labs in bioterrorism events.

Open Committee Discussion

Margo A. Smith, M.D., stated that she would like the gamma phage to be available but that controls and clinical guidance would have to be provided. **Valerie L. Ng, Ph.D., M.D.,** noted that her lab does not do phage testing and stated that competency and proficiency are important issues in making the phage available to Level A labs. **Dr. Ezzell** emphasized that the phage test should not be in the hands of people who have not been properly trained. **Ronald J. Zabransky, Ph.D.,** asked for clarification on the controls that could be placed on devices of different classifications, which **Steven I. Gutman, M.D., M.B.A.,** Director, Division of Clinical Laboratory Devices, provided. **Drs. Zabransky** and **Thrupp** suggested that fluorescent antibody testing might be appropriate for Level A labs because many such labs are used to conduct those tests, but **Dr. Ezzell** responded that fluorescent antibody testing for *B. anthracis* has many problems—for example, the capsule can cause background problems because it is always being sloughed off, and it is difficult to culture the organism. Panel members discussed the benefits of having a quick test versus the potential problems of test performance. **Drs. Ng and Thrupp** pointed out that if a patient has clinical manifestations of anthrax, treatment should not be delayed pending laboratory confirmation.

Panel Questions

Dr. Wilson then directed the Panel to the FDA's Questions. He noted that these questions are similar to those on the Classification Questionnaire form.

Question # 1: Are you aware of any other known risks to health presented by the uses of the types of devices identified by the FDA as preamendments reagents for the identification of *Bacillus anthracis*? Dr. Wilson summarized the panel's response in terms of safety around the issue of how the test was used and the clinical interpretations of the test.

Question # 2: Are you aware of any additional information which could affect the safety and effectiveness of the device? Dr. Wilson again summarized the panel's response as how to use the test results.

Question #3: What levels of controls are sufficient to provide reasonable assurance of the safety and effectiveness of these type devices? The panel agreed that General and Special Controls would be sufficient.

Question #4: Do you believe that restrictions on sale, distribution or use are necessary to provide reasonable assurance of safety and effectiveness?

Final Recommendations and Vote

Marjorie G. Shulman, Consumer Safety Officer, Center for Devices and Radiological Health, explained the classification questionnaire to the panel. Dr. Wilson asked the panel if they preferred to vote on each type device separately or bundle them. The panel voted 4-3 to consider the devices together. It voted unanimously to classify the devices in Class II and to recommend testing guidelines (Questions 1-3b).

Some panel members suggested that special controls could include reporting requirements. **Dr. Beavis** stated that regulations governing reporting should be left to the States. **Dr. Thrupp** expressed concern that if new strains and other problems were not reported, harm could result.

The panel voted 6-0 (with one abstention) to recommend that FDA partner with CDC, USAMRID, and other appropriate agencies involved in laboratory performance issues to develop practical ways to establish performance standards (Question 3b).

The panel also voted 7-0 for the FDA to place a high priority on establishing performance standards for the devices (Questions 4a and 4b). It voted 6-0 (with one abstention) that the devices should be restricted to use only by persons with specific training or experience in their use and only in certain facilities (i.e., that the devices should be limited in distribution and that accountability and oversight should be in the domain of public health laboratories) and that public health laboratories should be encouraged, in the context of the Laboratory Response Network, to develop appropriate training and reporting procedures for the devices (Questions 7a and 7b).

The panel then completed the Supplemental Data Sheet. The panel voted unanimously to accept the devices' current indications for use, with further amendments by FDA staff to develop an indication for the antigen and fluorescent antibody assays and to clarify the wording of the indication for the gamma phage reagent (Question 4). In response to question 5, the panel voted 6-1 to specify "as discussed" and to require that appropriate biosafety handling of the diagnostic specimens be followed. **Dr. Beavis** pointed out that *B. anthracis* is a Biosafety Level 2 organism and that it is incumbent upon laboratories to follow safe-handling procedures; the requirement was, in her opinion, unnecessary. In response to question 6, the panel voted unanimously to classify the devices as high priority. For questions 7, 8, and 9, the panel specified "as discussed," and in response to question 10, the panel

voted unanimously not to exempt the devices from any of the requirement listed. They responded to question 11 by specifying "as discussed." In its final vote, the panel voted unanimously to accept both forms.

FDA Presentation: *Y. pestis*

Ms. Shively described the *Y. pestis* preamendment products—a specific bacteriophage, antibody conjugates, and antigens for antibody detection—all of which aid in the diagnosis of pneumonic plague in humans. Ms. Shively provided background data on pneumonic plague; she noted that it is difficult to distinguish *Y. pestis* from *Y. pseudotuberculosis* in the laboratory.

Ms. Shively described each product and listed the factors affecting the results obtained with each product. Factors affecting bacteriophage results are the behavior of variant phage strains, the media used, the length and temperature of incubation, phage titer and stability, inoculum density, and the experience of the technologist.

Factors affecting fluorescent antibody test results are F-1 antigen expression by other species; variation in *Y. pestis* expression of F-1 antigen, which can be reduced as a result of storage and growth conditions; inoculum density; and the method of fixation.

Antigen preparation purity, concentration of F-1 antigen, the time at which the serum sample was obtained (i.e., if it was obtained too early), rare infections with nonencapsulated *Y. pestis,* and prozone effects can all affect antigen test results. In addition, the test cannot differentiate between recent and past infection, the endpoints are subjective, and heterophiles demonstrate nonspecific reactivity.

In concluding, Shively provided some information on the historical use of the three devices. She noted that although human disease is uncommon, *Y. pestis* is classified as a Category A critical biological agent: It can be easily disseminated and causes high mortality. Public health efforts continue to be important for preventing natural sources of infection.

Open Public Hearing

Rosemary Humes, representing the Association of Public Health Laboratories**,** emphasized that during the anthrax incidents last fall, much of what the public health labs had to deal with was environmental testing. In any bioterrorism event, people will be hysterical and will want environmental testing; the panel should consider this likelihood when discussing labeling and indications for use.

Dr. Wilson then invited the panel to ask questions of the speaker. **Dr. Reller** asked Ms. Humes several questions concerning the nature of the environmental testing that public health labs might be expected to conduct and how the labs dealt with demands from the public during the anthrax incident last fall. He stated that decisions regarding the role of public health labs should not be made in the political arena. **Ms. Humes** responded that in most cases, efforts were made to educate the public and turn them away from testing. Private environmental labs that did testing for the public could not rule out anthrax in some cases and thus had to send the samples to public health laboratories anyway.

Dr. Reller noted that *Y. pestis* is a fragile organism unlikely to generate the same issues of environmental testing as *B. anthracis*. FDA has an important role in educating everyone about actual risks. It is important to have competent laboratories, including public health laboratories that are adequately funded to do the job right, and to educate everyone, including politicians, on what really

protects the public's health and enables swift diagnosis for individual patients as well as swift public health responses to real events. **Dr. Thrupp** noted that Dr. Reller's comment suggested the same restrictions that the panel recommended for *B. anthracis,* which should serve to minimize the testing in private laboratories outside of the public health arena.

Dr. Thrupp asked who the suppliers of the reagents are, and **Dr. Ezzell** answered that the reagents are available from the Ft. Collins CDC laboratory or USAMRIID.

Irving Nachamkin, Dr. P.H., Hospital of the University of Pennsylvania**,** asked whether any performance data were available for the antibody and phage devices. **Dr. Ezzell** provided details on some of the factors that affect performance.

Open Committee Discussion

The panel felt that it had covered the main issues during the open public hearing.

Questions to the Panel:

Dr. Wilson then determined that the FDA questions would be answered when completing the Classification Questionnaire form, so the panel voted to answer them at that time.

Final Recommendation and Vote

The panel voted unanimously to consider the devices as a group. Dr. Wilson then led the panel through the classification questionnaire.

The panel voted unanimously to classify the devices in Class II and to require special controls like those for the *B. anthracis* devices: testing guidelines should be derived from available publications

and experience and should be developed for specimens, procedures, interpretation, and public health reporting (Questions 1-3b). The panel discussed issues involved in the enforcement of GMPs, in light of the limited distribution of the devices and FDA's enforcement capabilities, and voted unanimously to endorse the importance of FDA enforcement of GMPs for the devices.

Moving to Questions 7a and 7b, the panel voted unanimously that the devices should be used only by persons with specific training or experience in their use and only in certain facilities (i.e., that the devices should be limited in distribution and that accountability and oversight should be in the domain of public health laboratories). In addition, the panel voted 5-0, with one abstention, that public health laboratories should be encouraged to develop appropriate training and reporting procedures for laboratories using the devices.

The panel then completed the Supplemental Data Sheet. Panel members raised the issue of environmental testing devices and their relation to the FDA review process. The panel voted 6-0 to approve the current indications for use (Question 4); to note "as discussed" in response to question 5; to classify the devices as Class II with a high priority (Question 6); to specify "as discussed" in response to questions 7 and 8; to note "as discussed in question 7b of the Product Classification Questionnaire" in response to question 9; and to allow none of the exemptions listed in question 10. In its final vote, the panel voted unanimously to accept both forms.

Adjournment

Dr. Wilson thanked the participants and adjourned the meeting at 4:19 p.m.

I certify that I attended the meeting of the Microbiology Devices Panel on March 7, 2002, and that this summary accurately reflects what transpired.

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Freddie Mae M. Poole
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Michael L. Wilson, M.D.
Panel Chair

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